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10/822,006	04/12/2004	Akira Yamamoto	P24816	1571
7055	7590	07/24/2007	EXAMINER	
GREENBLUM & BERNSTEIN, P.L.C. 1950 ROLAND CLARKE PLACE RESTON, VA 20191				SINGH, SATYENDRA K
ART UNIT		PAPER NUMBER		
1657				
NOTIFICATION DATE		DELIVERY MODE		
07/24/2007		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com  
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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/822,006	YAMAMOTO ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Satyendra K. Singh	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 08 May 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 31-34,36,37 and 48-50 is/are pending in the application.
- 4a) Of the above claim(s) 1-30 and 39-47 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 31-34,36,37 and 48-50 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 12 April 2004 is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/8/2007</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
|   | 6) <input type="checkbox"/> Other: _____.                         |

## DETAILED ACTION

Applicant's response and amendments to the claims filed with the office on May 8<sup>th</sup> 2007 is duly acknowledged.

Claims 1-30 and 39-47 (inventions of group I and III) are withdrawn from further consideration.

Claims 35 and 38 have been canceled by applicant's current amendments to the pending claims.

Claims 31-34, 36-37, and newly added claims 48-50 (elected invention of group II; cell culture carriers having magnetic particles) have been examined on their merits in this office action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 31-34, 36-37, and 48-50 (as currently amended) is rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 31 recites "a coating layer containing a calcium phosphate-based compound as a **main component** thereof", which is ambiguous. It is not clear as to what proportion or amount of the calcium phosphate-based compound is required by the limitation as claimed, and as to what proportion of any other constituents or components are permitted by such claimed limitation. The meets and bounds of the invention as claimed are not defined in the claim as well as the instant disclosure provided by the applicants,

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and thus, the use of term “main component” renders the claimed invention indefinite. Appropriate explanation/correction is required. For examination purposes herein, the term “**main component**” has been construed to its general meaning of the word (“principal” or “chief” or **for the most part**, as indicated in Merriam-Webster online dictionary; [U]) that means a coating layer being made of **more than 50%** of a calcium phosphate-based (CaP) compound, as claimed.

Applicant’s arguments (see remarks for the previous rejection of claim 35, page 11, 3<sup>rd</sup> paragraph, in particular) regarding the term “mainly” (in the canceled claim 35) and currently used in the form of “a main component” in instant claim 31, is not found to be persuasive because it is unclear as to how the “main component” is to be understood by a person of ordinary skill in the art. For example, the term “main component” could be interpreted to mean “main component” in terms of volume, or “main component” in terms of weight, or “main component” in terms of mass, or any other type of variable that encompasses structural and/or physical features of the claimed cell culture carrier. Appropriate correction/explanation is required.

Since, claims 32-34, 36-37, and 48-50 depend (directly or indirectly) from the broader claim 31, they are also rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Claims 31-34, 36-37, and 48-50 (as currently amended) are rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim

31 recites “a coating layer containing calcium phosphate-based compound as a main component thereof”, which is ambiguous. It is not clear as to how many other “main components” are part of the coating layer, as presented in the claimed invention. The meets and bounds of the invention as claimed are not defined in the claim as well as in the instant disclosure provided by the applicants, and thus, the use of term “a main component” renders the claimed invention indefinite. Appropriate explanation/correction is required. For examination purposes herein, the term “ a main component” has been construed to mean that the coating layer is made of a calcium phosphate-based compound (in amounts, at least 50% or more), that covers at least a part of the surface of the base body.

Since, claims 32-34, 36-37, and 48-50 depend (directly or indirectly) from the broader claim 31, they are also rejected under 35 U.S.C. 112, second paragraph, as being **indefinite** for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 31-34, 36-37 and 48-50 (as currently amended) are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Starling et al (US Patent 6,210,715 B1; [A]) or Kitano et al (US Patent 5,540,995; [B]) in view of Nilsson et al (GB 2,093,040A, published as WO 82/00660; IDS).

Claims are generally directed to **cell culture carriers** (useful for anchorage-dependent cell cultivation) comprising a **magnetic particle** having a base body having a surface, the base body formed by compounding a resin material and a magnetic material so that the magnetic material is dispersed in the resin; and a **coating layer** containing a calcium phosphate-based compound as the main component, the coating layer being provided to cover at least a part of the surface of the base body of the magnetic particle.

Starling et al [A] teach cell culture carriers to which cells are allowed to adhere to and grow on surfaces thereof, wherein each of the carriers comprise glass or polymeric (such as polystyrene, polyethylene, dextran, gelatin, and/or glass) beads (suspendable or non-suspendable microspheres; solid or hollow; see Starling et al, abstract, summary of the invention, figures 1-1 and 1-2, column 10, 1<sup>st</sup> paragraph, in particular) that can be coated with a layer of calcium phosphate-based compound (CaP, such as hydroxyapatite, ticalcium phosphate, or other CaPs; see Starling et al, column 4, lines 1-3, in particular) to cover at least a part of the surface of the microspheres so that the cells are allowed to adhere thereto (also see Starling et al, examples 1-7, example 3 in

particular); wherein the cell culture carriers have an average particle size in the range of 100 microns to 6000 microns, wherein the density of the carriers is in the range of 1.2 to 2 g/cc (which can be varied depending on the components of the microbeads and various desired applications; see Starling et al, column 3, lines 47-50, and examples 1-13, in general); wherein the coating layer is formed from porous particles of calcium phosphate-based compound using suitable processes such as spray granulation or disk pelletization (that are well known in the art; see Starling et al, column 16, last paragraph, in particular), and are sintered such that the porous fine particles of CaP-based compound are partially embedded onto the surface of the polymeric microbeads (see Starling et al, examples 3-4, in particular), and provide increased surface area for greater activity in cell culturing applications (see Starling et al, column 17, lines 2-8, in particular).

Kitano et al [B] teach granular polymer composites (average particle size within the range of 1.2 to 30 microns; see abstract, summary of the invention, examples 1-7, and claims, in particular) comprising polymer beads (thermoplastic resins such as nylon, polystyrene, PMMA or polyethylene; see column 3, 2<sup>nd</sup> paragraph, in particular) having coated on the surface thereof a calcium phosphate-based compound (such as hydroxyapatite; see Kitano et al, column 3, last paragraph, in particular) such that the microcarriers or microbeads are suitable for allowing cells to adhere onto their surface (and thus suitable for the cell culture and/or related medical and diagnostic applications); wherein the coating layer is formed of fine porous CaP particles that are partially embedded/penetrated into the polymeric microbeads at the vicinity of the

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surface thereof (see Kitano et al, column 2, lines 10-16, in particular) using a process that requires colliding porous CaP particles to the surface of the polymeric microbeads or microspheres (using Nara Hybridization system; see Kitano et al, column 5, 2<sup>nd</sup> paragraph, and examples 1-7, in particular); and wherein the density of the composite microcarriers range within 0.9 to 1.2 g/cc (see Kitano et al, column 3, lines 39-47, in particular).

However, a cell culture carrier comprising a **magnetic particle** in combination with a polymeric resin material, having a surface that can be coated with **CaP-based compound** (as recited in the instant claim 31), is not explicitly disclosed by the teachings of Starling et al or Kitano et al.

Nilsson et al (IDS) teach cell culture carriers (microcarriers, suitable for use in the immobilization and cultivation of anchorage-dependent animal cells in and on the surface of the carriers; see Nilsson et al, WIPO document, abstract, page 1, 1<sup>st</sup> paragraph, in particular) comprising a magnetic particle (consisting essentially of a ferrite,  $\text{Fe}_3\text{O}_4$ ) having a surface, and a coating layer of gelatin or chitosan polymers (that can be cross-linked for improving mechanical strength of the microcarrier beads), and wherein the carriers have a particle size in the range of 100 to 250  $\mu\text{m}$  (see Nilsson et al, pages 10-11, and claims, in particular). The limitation of claim 33 is also met by the prior art, Nilsson et al because the ratio A/B (as defined in the instant claim 33; and taking the length of an average eukaryotic animal cell used for *in vitro* culture, to be in the range of 10-30  $\mu\text{m}$ ) taught by the prior art (i.e. beads/microcarriers of average

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particle size 100- 250  $\mu\text{m}$ ; results in an approximate ratio of A/B to be in the range of 5-50) meets the limitation of the invention as claimed.

It would have been obvious to a person of ordinary skill in the art at the time this invention was made to incorporate magnetic particles (as taught by Nilsson et al) into the polymeric microbeads or cell culture composition of Starling et al or Kitano et al such that the cell culture carriers have a magnetic particle having a surface, and a coating layer formed of porous, particulate CaP-based compound so that the cells are allowed to adhere to the surface thereof.

A person of ordinary skill in the art would have been motivated to modify the composition of Starling et al or Kitano et al by incorporating the magnetic particles in the microbeads, because Nilsson et al discloses the benefits of incorporating magnetic particles (such as  $\text{Fe}_3\text{O}_4$ ) in the microcarriers in order to permit the use of an external magnetic field to stir, suspend and/or isolate the microcarriers (see Nilsson et al, abstract, in particular).

One of ordinary skill in the art would have had a reasonable expectation of success in modifying the cell culture microcarriers of Starling et al or Kitano et al using the teachings of Nilsson et al as they explicitly disclose the process of making such microcarriers (that are suitable for cell culture applications) by incorporating  $\text{Fe}_3\text{O}_4$  particles in cross-linked gelatin beads (see Nilsson et al, pages 10-11, in particular).

The limitations of newly added claims 48-50 (wherein the magnetic material is present only in the vicinity of the surface of the base body; and wherein the average particle size of the magnetic particle is defined as C, C/A is 0.02 to 10) would have been

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obvious to an artisan of ordinary skill, given the fact that use of ferrite (such as Fe<sub>3</sub>O<sub>4</sub>) in the microcarriers (suitable for cell attachment and growth) are explicitly disclosed by the cited prior art (Nilsson et al), and therefore, such structural rearrangements and particle size of the magnetic particles (see the disclosures from Starling et al, and Kitano et al, above) would have been a matter of routine optimization for a person of ordinary skill in the art. In the absence of any evidence to the contrary, an artisan of ordinary skill would have a reasonable expectation of success in modifying the carrier as disclosed by Starling et al and Kitano et al (in view of Nilsson et al) because all the components (and the method steps) are disclosed in the cited prior art, as discussed above.

Thus, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill in the art at the time the claimed invention was made.

As per MPEP 2144.06, "*It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.*" *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

As per MPEP 2144.05 [R3], II. OPTIMIZATION OF RANGES - A. Optimization Within Prior Art Conditions or Through Routine Experimentation: *Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.*" *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

### **Obviousness-type Double Patenting**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the

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conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-34, 36-37 and 48-50 (as currently amended) are/remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/190,868 (common inventor and same assignee, PENTAX Corporation, Tokyo, Japan). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in the co-pending application are also directed to **a cell culture carrier** having a surface to which cells are allowed to adhere and grow, which is mainly made of a **resin** material that can comprise a **magnetic** material, and the surface of said carrier can be coated with a **calcium phosphate**-based compound, wherein the particle size and the **density** of each of the cell culture carriers is in the range of 10 to 2000  $\mu\text{m}$  and 1.01 to 1.5 g/cc, respectively (see specific recitations of claims 1-5, 8, and 10 of the copending application 11/190,868). The two sets of claims are clearly co-extensive, and therefore, an obviousness-type double patenting rejection is proper.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Response to Arguments***

Applicant's arguments filed with the office on May 8<sup>th</sup> 2007 (as they pertain to the prior art rejections of record) have been fully considered but they are not persuasive for the following reasons of record. The instant claims are generally directed to cell culture carriers (useful for anchorage-dependent cell cultivation; product-by-process claims) comprising a magnetic particle having a base body with a surface (the base body formed by compounding a resin material and a magnetic material so that the magnetic material is dispersed in the resin); and a coating layer containing a calcium phosphate-based compound as the main component, the coating layer being provided to cover at least a part of the surface of the base body of the magnetic particle.

Applicant's arguments are mainly focused on the following three points (see remarks, page 13-15, in particular): a) the presence of all claimed elements; b) the motivation to combine the separate reference teachings, and c) a reasonable expectation of success (see remarks, page 13, 5<sup>th</sup> paragraph, in particular), and state that "the office fails to establish any of these requirements" needed to establish a *prima facie* case of obviousness.

The cited prior art references (Starling et al, or Kitano et al in view of Nilsson et al) relied upon by the Examiner in the obviousness rejection of record (see also discussion above) disclose various cell culture carriers (in the form of microbeads, or microcarriers; suitable for attachment of cells and for anchorage-dependent cell cultivation) that can be formed of polymeric beads (such as resin materials) and can be coated with porous, calcium phosphate-based compound, that can be modified (in view

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of Nilsson et al) to include a magnetic material (as Nilsson et al disclose the benefits of incorporating magnetic particles in the microcarriers such as permitting the use of external magnetic field to stir, suspend and/or isolate the microcarriers; see Nilsson et al, abstract, in particular). Since, all the elements of the claimed invention are disclosed in the prior art including the process of compounding a resin material or polymeric beads with porous CaP particles (see Kitano et al, use of Nara Hybridization system to incorporate a coating layer of CaP; column 5, 2<sup>nd</sup> paragraph, and examples 1-7, in particular) that can be likewise used by one of ordinary skill in the art for incorporating the magnetic material, and thus for successfully modifying the cell culture carriers disclosed by Starling et al or Kitano et al. In the absence of any evidence to contrary, the cell culture carriers disclosed by the prior art references (Starling et al or Kitano et al in view of Nilsson et al) meet all the limitations of the instant invention as claimed, and therefore, the obviousness rejection of record over the pending claims is properly maintained.

### ***Conclusion***

**NO claims are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Satyendra K. Singh  
Patent Examiner  
Art Unit 1657

SANDRA E. SAUCIER  
PRIMARY EXAMINER